AF/1646
IFW

Docket No.: 350292000800
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Masahiko MIHARA et al.

Application No.: 09/381,598

Filed: September 20, 1999

Art Unit: 1646

For: PREVENTATIVES OR REMEDIES FOR SENSITIZED T CELL-RELATED DISEASES CONTAINING IL-6 ANTAGONISTS AS THE ACTIVE INGREDIENT

Examiner: J. Murphy

APPELLANT'S BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellant hereby appeals the final rejection of claims 14-22 and 33-38 communicated in the final Office action mailed March 11, 2003 and the Office communication mailed January 28, 2004. A Notice of Appeal was filed with a Petition for Revival on March 1, 2004, was received by the Office on March 1, 2004, and the Petition was granted on April 26, 2004, setting a time for response for this Appeal Brief to expire on May 31, 2004. This Brief is timely filed as it is submitted before August 26, 2004 with a petition for a two (2) month extension of time. Appellant has carefully reviewed the grounds for rejection and respectfully requests that the rejection of pending claims 14-22 and 33-38 be reversed. In accordance with 37 C.F.R. § 1.192, this Brief is filed in triplicate and is accompanied by the required fee. A copy of the claims involved in the present appeal is attached as Appendix A.

I. REAL PARTY IN INTEREST

The present application is assigned to Chugai Seiyaku Kabushiki Kaisha, a Japanese Corporation.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Appellant, Appellant's undersigned attorney or assignee that will directly affect, or be directly affected by, or have a bearing on, the decision by the Board of Patent Appeals and Interferences in the presently pending appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 15 claims pending in application.

B. Current Status of Claims

Claims canceled: 1-13 and 23-32

Claims withdrawn from consideration but not canceled: None

Claims pending: 14-22 and 33-38

Claims allowed: None

Claims rejected: 14-22 and 33-38

C. Claims On Appeal

The claims on appeal are claims 14-22 and 33-38.

IV. STATUS OF AMENDMENTS

All amendments have been entered and have been under consideration by the Office as of the final Office action dated March 11, 2003.

V. SUMMARY OF INVENTION

Independent claim 14 is directed in part to a method of treating a sensitized T-cell mediated disease by administering to a patient an antibody directed against an interleukin-6 receptor (hereafter referred to as an "IL-6 receptor"). Claim 14 and dependent claims 33-38 specify that the sensitized T-cell mediated disease is multiple sclerosis, uveitis, chronic thyroiditis, delayed hypersensitivity, contact dermatitis, or atopic dermatitis. Dependent claims 15-22 further describe the antibody administered for the method of treatment.

VI. ISSUES

There is only one issue presented for review: whether claims 14-22 and 33-38 are obvious under 35 U.S.C. § 103 (a) over the combination of Gijbels *et al.* (*Molecular Medicine 1*: 1076-1551 (1995)) in view of Vink *et al.* (*J. Exp. Med. 172*: 997-1000 (1990)), and further in view of Samid (U.S. Patent No. 5,605,930).

VII. GROUPING OF CLAIMS

The pending claims may be considered as a single group.

VIII. ARGUMENT

The Office rejected claims 14-22 and 24-32 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gijbels *et al.* (1995) in view of Vink *et al.* (1990). The Office alleged the Gijbels document teaches administration of anti-IL-6 antibodies in the EAE model of multiple sclerosis, and acknowledged the document did not disclose administration of anti-IL-6 receptor antibodies. The Office alleged Vink taught administration of anti-IL-6 receptor antibodies and anti-IL-6 antibodies, and combined Vink with Gijbels. The stated motivation for combining the documents was the reported protective effect of the anti-IL-6 antibody for EAE discussed in Gijbels might also have a therapeutic effect for inflammatory conditions of the CNS, including MS. The Office cited Samid, specifically at column 66, lines 20-47, for an alleged teaching that IL-6 is a pleiotropic cytokine

playing a central role in immune responses and inflammatory processes, and concluded the claimed methods would be expected.

Appellant respectfully submits that no *prima facie* case for obviousness has been presented. The Office has not reviewed each of the cited documents in its entirety and has instead constructed the rejection by picking and choosing isolated, one-sided passages. By doing so the Office has not appreciated the full teachings of the documents, which report inconclusive and opposing results and highlight substantial unpredictability concerning IL-6 targeted therapies. After a careful review of the cited documents, it is apparent the combination fails to teach or suggest the claimed methods because (1) the primary document Gijbels provides no indication that administering an antibody directed to IL-6 receptor could be used to treat a sensitized T-cell disorder, (2) Vink also does not indicate a T-cell mediated disorder could be treated with an antibody that neutralizes IL-6, and teaches away from interchanging an antibody directed to IL-6 with an antibody directed to IL-6 receptor, and (3) Samid fails to teach or suggest IL-6 is involved in the sensitized T-cell mediated diseases, and highlights unpredictability for therapeutics targeting the molecule. Also, there was no motivation to combine the cited documents, and there was no motivation to try the claimed methods since there was no reasonable expectation of successfully implementing them.

For these reasons, discussed in greater detail below, the Office has not met its burden of establishing *prima facie* obviousness. Assuming *arguendo* that a *prima facie* case had been established, teachings away from the claimed methods in the cited combination and the concomitant unexpected success of these methods substantiate non-obviousness.

There is No Teaching or Suggestion of the Claimed Methods

A *prima facie* case of obviousness requires the satisfaction of three requirements. First, the combined documents must teach or suggest all of the claim limitations. Second, the documents must provide a suggestion or motivation to modify the teachings or combine the documents either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. Third, the documents must provide a reasonable expectation of success. MPEP § 2143. More specifically, the obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the

scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

The documents cited for an obviousness rejection should be considered as a whole and portions arguing against obviousness or teachings away from the claimed subject matter must be considered. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 USPQ 416 (Fed Cir 1986). It is impermissible within the framework of section 103 to pick and choose from any one document only so much of it that supports a given position, to the exclusion of other parts necessary for the full appreciation of what the document fairly suggests to one of ordinary skill in the art. *In re Wesslau*, 147 USPQ 391 (CCPA 1965).

For the claims to be obvious the cited documents must teach or suggest a method for treating a sensitized T-cell-mediated disease by administering an antibody directed against an IL-6 receptor. As Gijbels discusses a method of administering an antibody directed against IL-6 itself, not the IL-6 receptor, there must be some indication in the cited documents that the antibody used in Gijbels could be replaced by an antibody directed against the IL-6 receptor. Stated another way, the combination of cited documents should teach or suggest that a person of ordinary skill in the art would have treated a sensitized T-cell-mediated disease by targeting the IL-6 receptor. Appellant respectfully asserts the cited documents fail to teach or suggest these features, as described hereafter.

The Office's assertion began with the following description in Gijbels:

> The conclusion from these studies is that Abs to IL-6 are protective by neutralizing endogenous IL-6 activity, and hence that IL-6 has a pro-inflammatory affect in these models.

This statement does not by itself teach or suggest an antibody directed against IL-6 receptor would elicit a protective response. The Office failed to quote the next sentence in Gijbels, which demonstrates that results were inconclusive:

> However, there have been reports of increased levels of circulating IL-6 after administration of mAb to IL-6 in animals in which IL-6 production was produced . . . in a patient with plasma cell leukemia after anti-IL-6 treatment. We found increased levels of IL-6 bioactivity in serum of animals treated with mAb to IL-6 (emphasis added).

Thus, Gijbels could not predict how the IL-6 directed antibody performed its function, and whether the antibody even neutralized IL-6 activity. This unpredictability is reaffirmed by a statement in the abstract on page 795:

> Our study indicates that IL-6 plays an important role in autoimmune CNS inflammation. However, due to the complex nature of the *in vivo* interactions of administered antibodies, the disease-reducing effect of the anti-IL-6 antibodies could be caused by neutralization of IL-6 activity or by enhancement of IL-6 activity via induction of higher IL-6 levels in the CNS. (Emphasis added)

Gijbels concludes on page 804, left column, first paragraph:

> The net result of administration of Ab to a cytokine thus is dependent on the balance between two opposing effects (*i.e.*, neutralization and accumulation). These findings indicate that the mechanisms underlying *in vivo* effect of antibodies to cytokines are complex (emphasis added).

As can be seen from these quotations Gijbels could not predict how the antibody functioned. The document could not predict whether the antibody neutralized IL-6, interfered with an interaction between IL-6 and its receptor, or enhanced circulating levels of IL-6. Thus, the document provided no indication that blocking an interaction between IL-6 and its receptor would confer a protective or therapeutic effect. Thus, there is no teaching or suggestion in Gijbels that an

anti-IL-6 receptor antibody could have been utilized for the treatment of a sensitized T-cell mediated disorder due to the unpredictable effect of the administered antibody. The unpredictability in Gijbels was elucidated after reviewing the document in its entirety, rather than picking and choosing isolated statements from it. The Office may have identified this unpredictability presented in Gijbels if it had correctly reviewed the document it its entirety.

Vink does not cure the defects of Gijbels as it also fails to teach or suggest a method for treating a sensitized T-cell mediated disease by administering an anti-IL-6 receptor antibody. Specifically, Vink did not teach or suggest administering an anti-IL-6 receptor antibody could treat a sensitized T-cell-mediated disorder because the document is directed to treating plasmacytoma, a disease of plasma B-cells, not T-cells.

Vink also fails to cure the defects of Gijbels because it did not teach or suggest an antibody directed to IL-6 could be exchanged for an antibody directed to IL-6 receptor. For such a teaching or suggestion, the document would need to establish the two antibodies share common properties, and do not exert opposite effects. Vink actually teaches the latter - that the antibodies exert opposite effects in cells. Specifically, Vink teaches on page 999, right column, that the anti-IL-6 receptor antibody 15A7 induced partial necrosis of some tumors, while the anti-IL-6 antibody had no significant effect under the same experimental conditions. Thus, Appellant does not understand the Office's assertion that Vink teaches or suggests the antibodies are interchangeable.

There are at least two conclusions from the analysis so far. First, the Office has not presented or considered the full teachings of Gijbels since it quoted only one-sided portions of the document. Other portions of the document must be considered to understand its full teachings. The proper conclusion is that Gijbels could not predict the action of the administered antibody and provided no suggestion that the antibody interfered with an interaction between IL-6 and its receptor. Because of this unpredictability, there was no teaching or suggestion in Gijbels that administering an anti-IL-6 receptor antibody would treat a sensitized T-cell-mediated disease. Second, because Vink shows that an antibody directed against IL-6 receptor and an antibody against IL-6 itself are not interchangeable, Vink does not remedy the defects of Gijbels and the combination does not teach or suggest the claimed methods.

In addition to the combination of Gijbels and Vink, the Office also cited the combination of Gijbels and Vink with Samid for the rejection of claims 34-38. The Office alleged that Samid links abnormal expression of IL-6 with pathogenesis and/or symptoms of a variety of diseases. Samid, however, fails to teach that IL-6 expression is involved with the pathogenesis and/or symptoms of a T-cell-mediated disease, let alone a sensitized T-cell mediated disease. In the section cited by the Office at column 66, lines 20-47, Samid does not mention any of the sensitized T-cell mediated diseases listed in claims 14 and 34-38. Samid also fails to determine whether a disease should be treated by administering an antibody, specifically an antibody directed to an IL-6 receptor. Samid further highlights the unpredictability of treating a disease by targeting an IL-6 pathway because it teaches IL-6 has a variety of functions and is involved in a number of unrelated conditions. Accordingly, Samid fails to cure the defects of the combination of Gijbels and Vink, and in fact highlights the unpredictability of the claimed methods addressed in Gijbels.

There was No Reasonable Expectation for Successfully Arriving at the Claimed Methods

As noted above, claims are *prima facie* obvious only if the prior art provides a reasonable expectation for successfully practicing what is claimed (MPEP § 2143). Given the unpredictability of treating sensitized T-cell disorders with an anti-IL-6 receptor antibody, there was no reasonable expectation for successfully performing the claimed methods. Gijbels concluded that IL-6 targeted treatments were complex and unpredictable, and provided no reasonable expectation that a sensitized T-cell related disorder could be treated by targeting the IL-6 receptor. Vink showed that an antibody directed against IL-6 could not necessarily be replaced by an antibody directed against an IL-6 receptor. Samid never associated IL-6 activity with a sensitized T-cell mediated disease specified in the claims, and never suggested administering an antibody to treat such a disease. Samid bolstered the unpredictable nature of targeting IL-6 by reporting its extensive and pleiotropic effects. Accordingly, treating a sensitized T-cell mediated disease by targeting an IL-6 receptor was unpredictable, and therefore, there was no reasonable expectation for successfully performing the claimed methods.

If the Office was basing its obviousness rejection on the premise that it would have been obvious to try or attempt the claimed methods, this rationale cannot properly support *prima facie* obviousness. The rationale has been rejected by the Court of Appeals for the Federal Circuit (CAFC), which articulated the test as being whether the prior art suggested to one of ordinary skill in the art that the claimed subject matter could be carried with a reasonable likelihood of success (*e.g.*, *In re O'Farrell*, 7 USPQ.2d 1673, 1681 (Fed. Cir. 1988); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988); and *In re Geiger*, 2 USPQ.2d 1276, 1278 (Fed. Cir. 1987)). As explained above, the combination of cited documents does not suggest the claimed methods nor does it suggest a reasonable likelihood that the claimed methods could be practiced successfully. In particular, the cited combination does not suggest parameters of the claimed methods could be performed or exchanged with reasonable success: Gijbels provided no suggestion that a sensitized T-cell mediated disorder could be treated successfully by targeting an IL-6 receptor due to a large degree of unpredictability in the reported results, and Vink did not show that exchanging an anti-IL-6 antibody with an anti-IL-6 receptor antibody would be reasonably successful. Accordingly the combination of documents does not establish *prima facie* obviousness.

There was no Motivation to Combine the Cited Documents

As noted above, *prima facie* obviousness can only be found when there is a motivation to combine documents forming the basis of an obviousness rejection (MPEP § 2143). Appellant found there was no motivation to combine the cited documents based upon the rationale set forth in *In re Rouffett*, 47 USPQ.2d 1453 (Fed. Cir. 1998).

Attention is called to page 1458 of the *In re Rouffett* decision where the Court identified three possible bases for motivation to combine references. The first listed basis, "the nature of the problem to be solved," is not common here as the claims address methods for treating a sensitized T cell-mediated disease by administering an anti-IL-6 receptor antibody. Combining Gijbels with Vink does not advance the solution to this problem as Vink addresses methods of treating plasmacytoma, a disease of plasma B cells, not treating sensitized T cell-mediated diseases. Further, Gijbels only addresses treatment of EAE with an anti-IL-6 antibody, not an anti-IL-6 receptor antibody.

The second basis, "the teachings of the prior art," is not common either as there is no motivation provided by the documents themselves. As noted above, Vink reported an effect on plasmacytoma B-cells by administering an antibody specific to IL-6 receptor and did not establish such an antibody was useful for treating other diseases. Because the claims are directed to methods for treating sensitized T-cell diseases, the person of skill in the art would not have been motivated to apply the anti-IL-6 receptor antibody used to treat B-cell related diseases from Vink. Also, because Gijbels established no link between IL-6 suppression and the reported therapeutic effect in the EAE model, the person of ordinary skill in the art was not motivated to apply an anti-IL-6 receptor antibody to the EAE system. Thus, there is not enough in common between Gijbels and Vink to suggest a combination of the two documents.

The third basis is "the knowledge of persons of ordinary skill in the art." In order to apply this basis, the Court stated that it would be necessary to "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination" and concluded that "the Board merely invoked the high level of skill in the field of the art. If such a rote invocation would suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance."

Because Gijbels failed to establish a link between IL-6 suppression and the reported therapeutic effect in the EAE model, and because it was stated that there is a "complex nature" of the *in vivo* interactions of administered antibodies," the person of ordinary skill in the art would not have necessarily experimented with other antibodies, such as an anti-IL-6 receptor antibody. Also, the motivation stated by the Office could have led the person of ordinary skill to experimentally apply an anti-IL-6 antibody, not an antibody specific for the receptor, since Gijbels reported results using only the IL-6-directed antibody. Further, because the Vink disclosure suggested only that anti-IL-6 receptor antibodies might be useful for treating B-cell plasmacytoma, the person of ordinary skill did not appreciate that such an antibody could be utilized to treat other diseases, such as sensitized T cell-mediated diseases. Because the Office has not provided further evidence of the ordinary skill in the art, it is reasonable to conclude that the person of ordinary skill did not

appreciate the applicability of anti-IL-6 receptor antibodies to the treatment of sensitized T cell-mediated diseases until the present invention.

The CAFC commented that the knowledge of persons of ordinary skill in the art may be evidenced by certain references of special importance, *i.e.,* that one or both of the cited documents is so well known that anyone in the art would be familiar with the documents. An example would be the famous Kholer and Millstein paper on monoclonal antibody preparations. Clearly, neither Gijbels or Vink rise to this level.

Thus, it should be apparent that the required motivation for combining the cited documents is not present here according to the analysis in *In re Rouffett*.

There also is no motivation to combine the cited documents according to the reasoning extended in *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984). In *In re Lalu*, the Court held "the motivation is not abstract, but practical, and is always related to the properties or uses" one skilled in the art would expect from a composition if made. Here, the person of ordinary skill in the art did not expect the antibody directed against IL-6 utilized in Gijbels would have the same properties and uses as the antibodies directed against the IL-6 receptor discussed in Vink. Vink utilized the antibodies directed against IL-6 receptor for the purpose of treating plasmacytoma, which is a disease of plasma B cells not sensitized T cells, only the latter of which is claimed. Accordingly, the person of ordinary skill in the art would not have expected that antibodies used to treat diseases of plasma B cell would be useful for treating diseases of sensitized T cells.

Extending the rationale in *In re Lalu* to the combination of Gijbels and Samid, Samid failed to suggest that IL-6 expression levels are pertinent to T-cell-mediated diseases specified in the claims. Thus, the person of ordinary skill in the art had no reason to apply any of the teachings in Samid to teachings in Gijbels or Vink because each of the documents discusses different types of diseases.

Accordingly, there was no motivation to combine the cited documents.

The Rejection is not Founded on the Cited Documents

It has long been held that the suggestion and reasonable expectation of success for *prima facie* obviousness must be founded in prior art, not in Appellant's disclosure. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ.2d 1438, 1444 (Fed. Cir. 1991). The evidence presented above shows that the Office cited one-sided quotations from documents rather than considering them as a whole, there was no reasonable expectation for successfully performing the claimed methods, and the combined documents reported inconclusive and disjointed subject matter. Given these factors, it is respectfully submitted that the Office impermissibly constructed the combination based on Appellant's specification, not on the cited documents themselves. Accordingly, there has been no *prima facie* showing of obviousness.

The Claimed Methods were Unexpected

The evidence presented above weighs in favor of finding no *prima facie* showing of obviousness. Assuming *arguendo*, however, that a *prima facie* showing had been established, teachings away from the claimed methods in the cited combination and the concomitant unexpected success of these methods substantiate non-obviousness.

Objective evidence of non-obvious includes teachings away in the cited document from the claimed subject matter and these teachings away rebut any *prima facie* case of obviousness. A cited document must be considered in its entirety, including portions which would lead away from the claimed invention. *W.L. Gore & Associates, Inc., v Garlock, Inc.*, 721 F. 2d 1540, 1550, 220 USPQ 303 (Fed. Cir. 1983). The CAFC in *In re Gurley*, 27 F.3d 551, 553, 31 USPQ.2d 1130, 1131 (Fed. Cir. 1994) stated a "reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. Further, a finding that the claimed subject matter was unexpected is evidence of non-obviousness. *In re O'Farrell*, 7 USPQ.2d at 1681: "[t]here is always at least a possibility of unexpected results that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious."

Vink discouraged the person of ordinary skill from administering an anti-IL-6 receptor antibody to a subject to treat a sensitized T-cell mediated disorder. Vink provided evidence that an anti-IL-6 antibody and an anti-IL-6 receptor antibody were not necessarily interchangeable, and therefore, a person of ordinary skill in the art would not have exchanged the antibody discussed in Gijbels with an anti-IL-6 receptor antibody. And Vink provided no evidence that an anti-IL-6 receptor antibody would have any affect on a sensitized T-cell mediated disease since the disclosure was limited to treatments of B-cell related disorders. As Gijbels and Samid showed that treating IL-6 related disorders was complex and unpredictable, the totality of the evidence in the cited combination discouraged the person of ordinary skill in the art from practicing the claimed methods. This discouragement and unpredictability in the field made the success of the claimed methods unexpected. Thus, the successful practice of the claimed methods was unexpected and non-obvious.

IX. CONCLUSION

Appellant has addressed the rejection alleged by the Office and respectfully submits that the final rejection of the pending claims under 35 U.S.C. § 103(a) is in error and requests reversal of this rejection by the Board. The totality of the record weighs in favor of a finding of non-obviousness by a preponderance of the evidence.

A copy of the claims involved in the present appeal is attached as Appendix A.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Appellant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 350292000800. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 12, 2004

Respectfully submitted,

By _____

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sd-196762

APPENDIX A

Claims Involved in the Appeal of Application No. 09/381,598

Claims 1-13 (Cancelled)

Claim 14. (Previously Amended): A method for treating a sensitized T cell-mediated disease, which comprises administering to a patient in need thereof a pharmaceutical composition comprising an antibody directed against interleukin-6 (IL-6) receptor and a pharmaceutically acceptable carrier, wherein the sensitized T cell-mediated disease is multiple sclerosis, uveitis, chronic thyroiditis, delayed hypersensitivity, contact dermatitis, or atopic dermatitis.

Claim 15. (Previously Amended): The method according to claim 14, wherein the antibody directed against the IL-6 receptor is a monoclonal antibody.

Claim 16. (Previously Amended): The method according to claim 15, wherein the monoclonal antibody is directed against the human IL-6 receptor.

Claim 17. (Previously Amended): The method according to claim 15, wherein the monoclonal antibody is directed against the mouse IL-6 receptor.

Claim 18. (Previously Amended): The method according to claim 16, wherein the monoclonal antibody is the PM-1 antibody.

Claim 19. (Previously Amended): The method according to claim 17, wherein the monoclonal antibody is the MR16-1 antibody.

Claim 20. (Previously Amended): The method according to claim 16, wherein the monoclonal antibody has the constant region of a human antibody.

Claim 21. (Previously Amended): The method according to claim 16, wherein the monoclonal antibody is a chimeric or humanized antibody directed against the IL-6 receptor.

Claim 22. (Previously Amended): The method according to claim 21, wherein the monoclonal antibody is a humanized PM-1 antibody.

Claims 23-32 (Cancelled)

Claim 33. (Previously Presented): The method of claim 14, wherein the T cell-mediated disease is multiple sclerosis.

Claim 34. (Previously Presented): The method of claim 14, wherein the T cell-mediated disease is uveitis.

Claim 35. (Previously Presented): The method of claim 14, wherein the T cell-mediated disease is chronic thyroiditis.

Claim 36. (Previously Presented): The method of claim 14, wherein the T cell-mediated disease is delayed hypersensitivity.

Claim 37. (Previously Presented): The method of claim 14, wherein the T cell-mediated disease is contact dermatitis.

Claim 38. (Previously Presented): The method of claim 14, wherein the T cell-mediated disease is atopic dermatitis.